# Startle Seizures and Diffuse Leukoencephalopathy After Resolution of Herpes Simplex Virus 1 Encephalitis in a Child

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## Abstract

We describe a unique clinical presentation of a child after the acute phase of herpes simplex virus 1 (HSV1) encephalitis. A 17-month-old boy first presented with HSV1 encephalitis and was promptly treated with antiviral medication. Seven months later, he was re-admitted for startle seizures. Magnetic Resonance Imaging of the brain showed diffuse confluent leukoencephalopathy. This constellation of symptoms has not been previously reported in HSV1 encephalitis. In conclusion, we showed that brain injury due to HSV1 encephalitis can be associated with the development of startle seizures and diffuse white matter injury in the post-acute phase.

## Keywords

startle seizures, reflex seizures, epileptic spasms, herpes simplex virus 1, encephalitis, leukoencephalopathy

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## Introduction

Postencephalitic epilepsy is characterized by the enduring predisposition to have seizures after the acute phase of encephalitis. This structural epilepsy is characterized by multifocal seizures and is associated with worse clinical outcomes.[1] Herpes simplex virus 1 (HSV1) is a common cause of postencephalitic epilepsy,[2] and HSV1 encephalitis is the most common cause of sporadic encephalitis. Clinical seizure patterns in postencephalitic epilepsy due to HSV1 are varied,[2] but are often focal in onset and intractable.[3] We herein report a unique case of startle seizures and leukoencephalopathy in the post-acute phase of HSV1 encephalitis, adding to the currently reported clinical phenotype.

## Patient Description

A 17-month-old boy of Canadian First Nations, Cree descent with a history of prematurity (34-week gestation), mild speech delay, and immunizations only up to 2 months of age presented with a 40-minute-long focal status epilepticus in the context of a 7-day febrile viral prodrome. In his initial clinical exam, his Glasgow coma scale (GCS) was 8, and he was found to have right-sided tonic stiffening and diffuse hyperreflexia. These findings were thought to be due to ongoing seizure activity. Phenytoin 20 mg/kg was given as an intravenous load, and he was started on maintenance Levetiracetam at 40 mg/kg/day. Cerebrospinal fluid (CSF) studies performed on day 2 of admission revealed 103 white blood cells (WBC) (67% lymphocytes and 22% polymorphonuclear cells), 387 red blood cells (RBCs), glucose 3.4 mmol/L, protein 0.42 g/L, and positive HSV1 polymerase chain reaction (PCR). Magnetic Resonance Imaging (MRI) brain performed on day 3 of admission showed T2 hyperintensity and diffusion restriction in the right frontal and temporal lobes along with leptomeningeal enhancement, findings consistent with HSV1 meningoencephalitis (Figure 1A and B). Electroencephalogram (EEG) showed continuous right temporal

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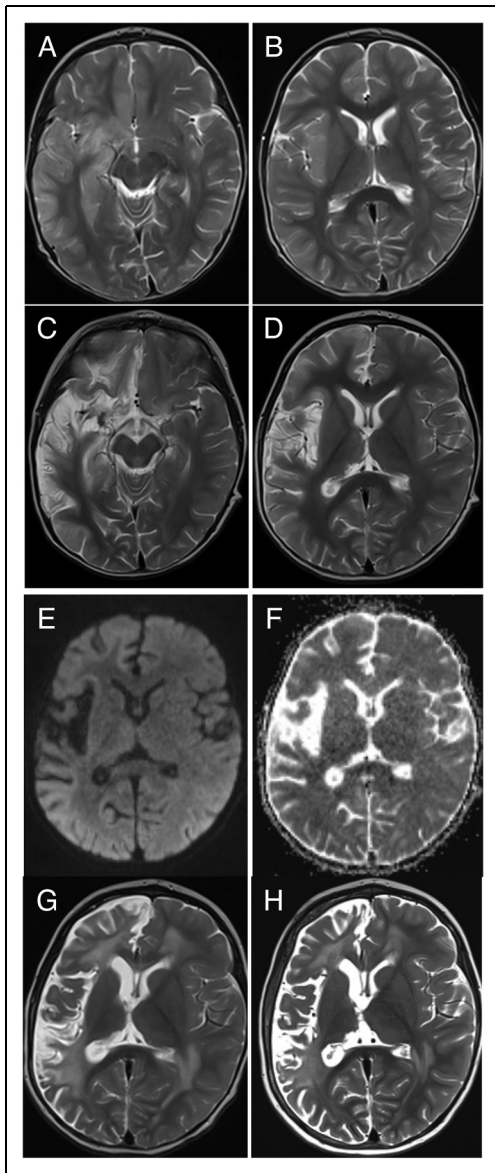Email: cng2@ualberta.ca

**Figure 1.** Axial MRI brain images. (A) and (B): MRI T2 sequences performed at day 3 of admission during acute HSV1 meningoencephalitis demonstrating thickening, edema, and T2 hyperintense signal, involving the right temporal lobe, right frontal lobe, right insular cortex, and right lentiform nucleus. (C) and (D): MRI T2 sequences performed at the end of Acyclovir treatment (day 21 of admission) demonstrating expected evolution of right temporal lobe and inferior frontal lobe signal abnormality with new findings of early encephalomalacia. (E) and (F): MRI Diffusion weighted imaging (DWI) B-800 and corresponding apparent diffusion coefficient (ADC) sequences performed at day 21 of admission showing lack of diffusion restriction in the white matter. (G) and (H): MRI T2 sequence performed 7 months and 15 months after HSV1 encephalitis, respectively, demonstrating new diffuse white matter changes sparing subcortical U-fibers. The white matter changes in the latter scan (H) did not significant change compared to the previous study (G).

slowing with no epileptiform discharges. He was treated with a 21-day course of intravenous acyclovir at 20 mg/kg/dose every eight hours. At the end of acyclovir treatment, CSF HSV1 PCR was negative, and repeat MRI brain (day 21) showed expected

encephalomalacia of the right temporal lobe and inferior frontal lobe with no corresponding diffusion restriction (Figure 1C to F). At the end of his hospital stay, he had residual left leg and arm hemiplegia and was discharged with outpatient follow up at a rehabilitation hospital. At this point, he was seizure-free on Levetiracetam, but the patient's family decided to discontinue this medication four days after discharge.

Seven months post treatment, he was admitted to the hospital with a 1.5-month history of language regression and new-onset paroxysmal events, which we identified as startle seizures. These events were provoked by sudden, loud sounds and were characterized as 1-second-long stiffening events with neck flexion, shoulder internal rotation, bilateral elbow extension, finger abduction, and hip adduction. He then subsequently relaxes his muscles over the following one second. There was no clear post-ictal state after these startle seizures. Ictal EEG showed generalized slow wave during the stiffening phase, followed by attenuation of background over at least eight seconds (video). Interictal EEG showed near continuous multifocal and bisynchronous epileptiform activity, which met the BASED criteria for hypsarrhythmia (BASED score = 5) (Figure 2).[4] MRI brain showed new diffuse confluent white matter changes sparing the U-fibres (Figure 1G). MRI C-spine did not reveal a cord lesion (data not shown). Repeat CSF studies were negative for WBCs, HSV1 PCR, and N-methyl-D-aspartic acid (NMDA) receptor antibodies. Screening studies for inborn errors of metabolism including serum amino acids, ammonia, lactate, acylcarnitine profile and urine organic acids, mucopolysaccharides, sialic acid, and homocysteine were negative. Whole exome sequencing revealed a variant of unknown significance in the *HCFC1* gene. He was empirically treated with methylprednisolone 30 mg/kg daily for 5 doses. Discharge antiseizure regimen included valproic acid 47 mg/kg/day and clobazam 1 mg/kg/day. However, he continued to suffer from daily startle seizures at least in part due to difficulties administering medications as the child was spitting up the antiseizure medications daily. Subsequent serial MRIs performed up to fifteen months post treatment showed no further progression of the white matter changes (Figure 1G and H). By three years of age, he continued to have global developmental delay with on average two startle seizures daily. He walks with an ataxic gait. Although he had lost his language during the acute phase of HSV1 infection, he had regained some words and can combine two-word phrases. However, he cannot follow simple commands. He has no social overtures apart from approaching his parents for his needs. He continues to be followed by a multidisciplinary team involving pediatric neurology, developmental pediatricians, and speech language pathology every 3–6 months. His current antiseizure regimen include valproic acid 47 mg/kg/day and Clonazepam 0.18 mg/kg/day.

## Discussion

We described the first case of startle seizures and diffuse, nonprogressive leukoencephalopathy that developed after the acute phase of HSV1 encephalitis.
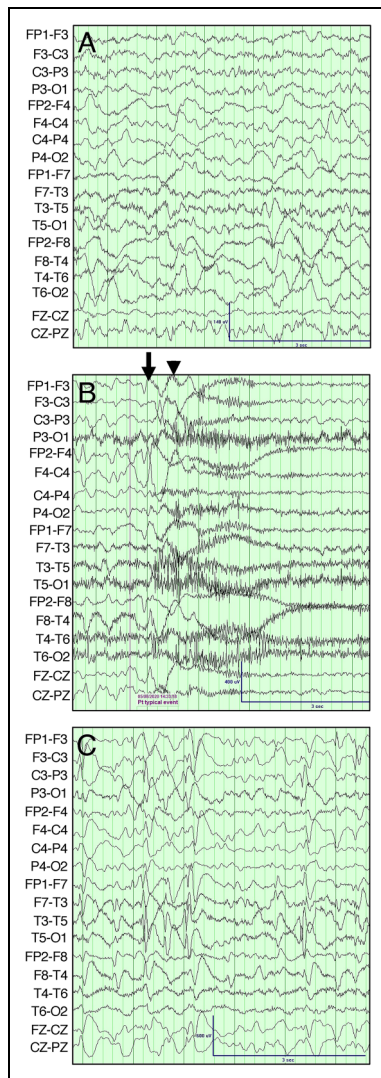
**Figure 2.** Electroencephalogram using the 10–20 system performed in the awake state. (A): Bipolar montage of the EEG performed at day 3 of admission during acute phase of HSV1 encephalitis. Note the continuous right temporal polymorphic delta slowing. Sensitivity setting is 7 uV/mm. (B): bipolar montage demonstrating a typical startle seizure. The technician startles the child with a clap (black arrow). The head flexion and onset of arm stiffening correlate with slow wave (arrowhead). This is followed by diffuse electrodecremental response. (C): Near continuous multifocal and bisynchronous epileptiform discharges seen interictally. Calibration bar is shown in the bottom right. Timebase of the EEG clips is 10 mm/sec. The sensitivity for (A), (B), (C) are 7 μV/mm, 20 μV/mm, 30 μV/mm, respectively. Low frequency filter of 1 Hz and High frequency filter of 70 Hz were applied. No notch filter was applied.

The representative EEG (Figure 2B) captured a startle seizure following an auditory stimulus (clap) produced by the EEG technician. The ictus was characterized by an ictal broad wave followed by an electrodecrement response. Although marred by muscle artifact, these electrographic features support the stiffening events as being epileptic in origin. Indeed, these seizures have the electrographic features and clinical semiology of startle epileptic spasms. Intracranial EEG, magnetoencephalography, and surgical

resection studies have suggested the involvement of the supplementary motor area and the mesial aspects of the frontal and parietal lobes in the generation of startle seizures.[5] However, the underlying network in the generation of startle seizures remains to be clarified.[6]

Reflex seizures refer to seizures that are constantly evoked by a specific stimulus, including the startle stimulus described herein. When occurring alone without other spontaneous seizures, this is referred to as reflex epilepsies. Reflex epilepsies can be idiopathic, such as reading epilepsies or can be associated with structural brain lesions, such as startle epilepsy.[7] Unfortunately, seizure control in startle epilepsy is often difficult.

Seizures can arise in the post-acute phase of HSV1 encephalitis due to relapse of HSV1 infection, postinfectious autoimmune disease, and classic postencephalitic epilepsy.[8] HSV1 relapse occurs in 26% of patients treated for HSV1 encephalitis.[9] Symptoms usually occurs 1 week to 3 months after acyclovir treatment is stopped. The pathogenesis is likely due to inadequate treatment with acyclovir or impaired host immune responses.[10] Alternatively, postencephalitic autoimmune disease after HSV1 encephalitis can occur and often starts within 1 month. Postencephalitic autoimmune disease may present with seizures and movement disorders, such as choreoathetosis in the case of anti NMDA receptor encephalitis.[11] HSV1 PCR in CSF is accordingly negative in these cases.

In our patient, the relapse of HSV1 and autoimmune disease were not supported by the results of repeat CSF testing. The pathogenesis of postencephalitic epilepsy is unclear but it likely involves neuronal hyperexcitability, most often in the mesial temporal lobes.[8] In the Montreal series of patients with post HSV encephalitic epilepsy, 72% of seizures were characterized as focal-onset seizure with up to 52% of these having an extratemporal or multifocal foci.[12] Startle seizures after HSV1 encephalitis have not been previously reported. However, it had been described in patients with perinatal brain injury, traumatic brain injury, metabolic diseases, trisomy 21, and congenital brain malformations.[6,13] Interestingly, in the postencephalitic phase of the syndrome of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), startle seizures appear to be quite common.[3] AESD is a syndrome of acute encephalitis due to a viral trigger and is characterized by two phases of seizures and a characteristic appearance of widespread diffusion restriction of subcortical white matter with central sparing.

There have been reports of HSV1 encephalitis causing white matter changes in addition to extensive cortical involvement, likely explained by direct viral invasion, inflammation, and severe cerebral edema.[14,15] In our patient, the diffuse confluent white matter signal change developed between the end of his acyclovir treatment (day 21 of his first admission) and seven months post treatment (Figure 1E). Markoula et al. reported a patient with insula and periventricular white matter T2 hyperintensity lesions post-HSV1 infection.[16] To our knowledge, the diffuse but selective involvement of our patient's supratentorial white matter without further cortical changes post-HSV1 infection has not been reported in other patients post-HSV1 infection. The lack of diffusion restriction in the white matter in the acute phase of

infection argued against an expected evolution of existing white matter damage (Figure 1C and D). The MRI appearance of confluent white matter involvement and the lack of unexplained encephalopathy, systemic findings and multifocal neurologic symptoms suggest against acute disseminated encephalomyelitis (ADEM). Instead, this pattern of involvement initially raised the possibility of a leukodystrophy, but whole exome sequencing and screening metabolic studies were unrevealing. CSF to plasma glycine ratio was unremarkable, arguing against Leukoencephalopathy with Vanishing White matter, a condition seen in some patients of Cree descent.[17] Interestingly, this pattern of selective white matter injury seen in our patient had been described in another severe type of epilepsy known as Febrile infection-related epilepsy syndrome (FIRES).[18] FIRES is a syndrome of refractory status epilepticus preceded by a known febrile infection without infectious encephalitis. The mechanism of white matter injury due to FIRES and other epileptic encephalopathies remains to be elucidated.

## Author Contributions

ACHN wrote the manuscript. ACHN, JK, HG, FMJ, and JM edited the manuscript and provided patient care. JM was the supervising author.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

## Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

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## Trial Registration

Not applicable, because this article does not contain any clinical trials.

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